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CITIZEN PETITION

The undersigned, on behalf of GlaxoSmithKline (GSK), submits this petition under 21 CFR 10.30 to request that the Commissioner of Food and Drugs (the Commissioner) refrain from approving abbreviated new drug applications (ANDAs) for topical mupirocin ointment products where the applicant cannot support all elements of the labeling approved for the reference listed drug (RLD).

A product approved under an ANDA must bear the same labeling, and must be approved for the same conditions of use, as the RLD product (*see infra*). If the labeling of a proposed drug product is materially different, the proposed product must be the subject of a new drug application (NDA), rather than an ANDA.

In December 2002, the Food and Drug Administration (FDA) approved a mupirocin ointment product sponsored by Clay-Park Labs, Inc. (Clay-Park) under section 505(b)(2) of the Food, Drug, and Cosmetic Act (the FDCA). The basis for the approval was a study comparing the Clay-Park product to Bactroban Ointment® (mupirocin ointment) in patients with impetigo. On this basis, FDA's Division of Anti-Infective Drug Products permitted Clay-Park to "reference" certain sections of the approved labeling

for Bactroban Ointment for use in treating impetigo.1/ Clay-Park, however, was not permitted to reference Bactroban Ointment's full "Microbiology" labeling. As a result, the labeling of the Clay-Park product is materially different from Bactroban Ointment.

GSK is petitioning to ensure that FDA applies the same scientific and regulatory analysis that formed the basis for the Clay-Park approval to all other mupirocin ointment products that seek approval based on a showing of bioequivalence to Bactroban Ointment.

A. ACTIONS REQUESTED

By this petition, the undersigned requests that the Commissioner refrain from approving mupirocin ointment products under section 505(j) of the FDCA where the applicant's bioequivalence data is substantially the same as that submitted in support of Clay-Park's application under section 505(b)(2) of the FDCA. Absent additional data to support the full labeling of the RLD product, the petitioner requests that the Commissioner require the submission of a new drug application (NDA) pursuant to section 505(b) of the FDCA for the approval of any new topical mupirocin ointment product. The undersigned also requests that the Commissioner enforce the regulatory requirement, under 21 CFR 320.24(b)(2), that a showing of bioequivalence based on comparative clinical studies must include more than one independent, adequate and well-controlled study.

B. STATEMENT OF GROUNDS

1. Background

In December 1987, FDA approved Bactroban Ointment® (mupirocin ointment), 2%, for use in the topical treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*. Bactroban Ointment consists of mupirocin, a naturally occurring antibiotic, in a polyethylene

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1/ This petition takes no position on the possible reliance by Clay-Park or FDA on the prior approval of Bactroban Ointment. *See generally* FDA Docket No. 01P-0323/CP1 (petition challenging FDA's interpretation of section 505(b)(2) of the FDCA). GSK lacks sufficient information at this time to assess that issue.

glycol (PEG) ointment base. GSK markets the product, along with an intranasal version and a cream, both of which contain a calcium salt of mupirocin.

Mupirocin is an antibacterial agent produced by fermentation using the organism *Pseudomonas fluorescens*. The labeling for Bactroban Ointment states that the product is active against a wide range of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), and certain Gram-negative bacteria. *See* Tab 1, Labeling for Bactroban Ointment (Microbiology section). The labeling also states that, based on *in vitro* data, the product is active against most strains of *Staphylococcus epidermis* and *Staphylococcus saprophyticus*. *Id.* The current labeling, including the MRSA labeling, was extensively revised at the request of the agency's Division of Anti-Infective Drug Products to conform to the labeling of two other Bactroban products, Bactroban Cream and Bactroban Nasal.2/

In December 2002, Clay-Park received approval under section 505(b)(2) for a mupirocin ointment, 2%, product. Tab 3, Approval letter (NDA 50-788). Like Bactroban Ointment, the Clay-Park product was approved "for the topical treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*." *Id.* Unlike Bactroban Ointment, Clay-Park's product is formulated without a PEG base.

Clay-Park's approval was based on a comparative, parallel-group study (with 475 evaluable patients) in which the Clay-Park product was compared against Bactroban Ointment in patients with impetigo. *See* Tab 4, Labeling for Clay-Park Mupirocin Ointment (Clinical Studies section). At one week post-therapy, 94% of the Clay Park patients met the primary "clinical success" endpoint, compared with 95% of the Bactroban Ointment patients. *Id.* at 5. With respect to safety, the incidence of adverse events was reported to be comparable for the two products. *Id.* Based on this study, the

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2/ *See* Tab 2, Approval Package for NDA 50591/S022 (April 22, 1999), including Clinical Microbiology Review Notes (HFD-520) (May 7, 1998) (setting forth recommended labeling for Bactroban Ointment); Facsimile from FDA Division of Anti-Infective Drug Products (Jan 21, 1999) (requesting revisions to Microbiology section of labeling of Bactroban Ointment).

agency apparently determined that the two products are clinically equivalent when used to treat impetigo.

The agency, however, did not approve labeling for the Clay-Park product that is the same as the labeling for Bactroban Ointment. Significantly, the "Microbiology" section of the approved labeling for Clay-Park's product is materially different from Bactroban Ointment. *Compare* Tab 1 and Tab 4. Among other differences, the Clay-Park labeling does not state that the product is active against MRSA. Tab 4 at 1-2 (Microbiology section). It also states that the product is active, *in vitro* only, against certain Gram-negative bacteria. And, the labeling does not state that the product is active, *in vitro*, against strains of *Staphylococcus epidermis* and *Staphylococcus saprophyticus*. *Compare* Tab 1 and Tab 4.

The agency has assigned a "BX" therapeutic equivalence code to these "multisource" products. *See Approved Drug Products with Therapeutic Equivalence Evaluation* (the "Orange Book") (23rd ed. 2003). FDA, therefore, does not consider Bactroban Ointment and Clay-Park's mupirocin ointment to be substitutable. Although the agency has not disclosed its reasoning, a review of the approved labeling strongly suggests that FDA considered the difference in Microbiology labeling, including the difference in MRSA labeling, to be material to the therapeutic equivalence determination. 3/

2. The Drug Approval Process

Under section 505(j) of the FDCA, the agency is authorized to approve drug products without an independent showing of safety and effectiveness, provided the product is shown to be "the same as" a "listed" product previously approved under sections 505(c) or 505(j). A product approved under section 505(j) must be approved for the same conditions of use, and must bear the same labeling, as the listed product referenced in the application. 21 USC 355(j)(2)(A)(i) and (v); 21 USC 355(j)(4); 21 CFR

3/ FDA has yet to release the summary approval documents to the public under the Freedom of Information Act (FOIA). Thus, this analysis is based on a comparison of the labeling for the Clay-Park product and Bactroban Ointment. Other discrepancies between the labeling of the Clay-Park product and Bactroban Ointment are due to differences in the clinical studies reported and product formulation. These differences ordinarily would not result in assignment of an inequivalence rating. 21 CFR 314.94(a)(8)(iv).

314.92(a)(1).4/ If data for the proposed product fails to support all elements of the reference drug's labeling, the product cannot be approved under section 505(j). Instead, a product with labeling that differs materially from the reference drug may only be approved on the basis of an NDA under section 505(b). *See* 21 USC 355(j)(4)(G); 21 CFR 314.127(a)(7).

In addition to the "same labeling" requirement, a product approved under section 505(j) must, among others, be "bioequivalent" to the reference product. 21 USC 355(j)(2). Bioequivalence is defined in the statute to mean that:

> the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . . .

21 USC 355(j)(8)(B). The bioequivalence requirement for ANDA approval applies both to locally and systemically absorbed drug products. *See* 57 FR 17950, 17972 (April 28, 1992).

Applicants must show bioequivalence using "an accurate, sensitive, and reproducible approach" that has been shown to be capable of demonstrating the bioequivalence of the test product. 21 CFR 320.24(a). FDA previously issued a draft guidance defining a method for demonstrating the equivalence of topical products based on objective pharmacokinetic (PK) measures (*i.e.*, measures of the rate and extent of absorption, distribution, and metabolism of the active ingredient). The method, known as dermatopharmacokinetics (DPK), was withdrawn last year in response to scientific concerns regarding the validity of the methodology. 67 FR 35122

4/ Some minor differences in labeling are permitted, for example to identify different manufacturers. *See* 21 USC 355(j)(2)(A)(v). These differences are enumerated by regulation under 21 CFR 314.94(a)(8)(iv). If any such labeling difference would render the proposed product less safe or less effective for the conditions of use for which it will be labeled, the product cannot be approved under an ANDA. *See* 21 CFR 314.127(a)(7). *See also* 54 FR 28872, 28884 (July 10, 1989) (the agency "will not accept ANDAs for products with significant changes in labeling").

(May 17, 2002). No other surrogate method for demonstrating bioequivalence of topical drug products has been accepted or validated by the scientific community. *See generally* FDA Advisory Committee for Pharmaceutical Science (Mar. 12, 2003) (the "ACPS Transcript") (available at www.fda.gov). Thus, sponsors of topical drug products under section 505(j) must show equivalence through "appropriately designed comparative trials." *See* 21 CFR 320.24(b)(4).

FDA has yet to issue any guidance on the use of clinical studies to show bioequivalence for topical products. As a senior FDA official recently noted, "We have struggled for the last 12 years trying to develop a method for assessing bioequivalence of drugs applied to skin and we have not been successful in trying to move that decision forward in a consensus way." ACPS Transcript at 51 (statement of Ajaz Hussain, Ph.D.).

One point that is clear, however, is that the existing regulations require sponsors to conduct at least two independent "trials" to establish bioequivalence based on clinical endpoints. 21 CFR 320.24(b)(4) (specifying that at least two "clinical trials" are required). These studies involve the treatment of patients with both a test and a reference product according to the approved labeling of the reference product. When relying on this method, rather than on surrogate or analytical methods, the regulations make clear that a second *independent* study is needed to validate the results of the first study. *Id.* This is because clinical endpoints are significantly more variable than pharmacokinetic endpoints (*see infra).*

3. Discussion

a. The "Same Labeling" Issue

As discussed above, the agency recently approved a mupirocin ointment product based on bioequivalence data, comparing a test product (by Clay-Park) against a reference product (Bactroban Ointment). FDA approved the Clay-Park product for the same primary indication (*e.g.*, topical treatment of impetigo due to *Staphylococcus aureus* and *Streptococcus pyogenes*), with the same labeling as Bactroban Ointment for that condition of use.

The agency, however, declined to approve the same "Microbiology" labeling for the Clay-Park product. For example, the microbiology labeling for Bactroban Ointment states that mupirocin "is active against a wide range of gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA)."5/ The Clay-Park labeling does not describe activity against MRSA. Clay-Park's labeling also includes a statement that "[m]ethicillin resistance and mupirocin resistance commonly occur together in *Staphylococcus aureus* and coagulase negative staphylocci," suggesting that the absence of activity against MRSA may be clinically significant.

In short, the agency apparently determined that a showing of equivalence in patients with impetigo could only support the same labeling for that indication; the data could not be extended to labeling for other conditions of use, including the discussion of other pathogens identified in the Microbiology section of the approved labeling. This limitation on the use of the primary showing of bioequivalence must be applied to all other similar mupirocin ointment products that seek approval, either under 505(b)(2) or 505(j), based on a reference to Bactroban Ointment.6/

The application of this analysis is especially significant for products that seek approval under section 505(j). As discussed, such products must be approved with the same labeling as Bactroban Ointment. 21 USC 355(j)(2)(A)(v) and 355(j)(4)(G). The "same labeling" requirement is a necessary condition for approval of an ANDA under section 505(j). Based on the Clay-Park decision, an ANDA applicant with clinical data in support of the impetigo indication will be unable to satisfy the statutory "same labeling" requirement. Such an applicant, like Clay-Park, cannot reference the full,

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5/ As noted above, FDA requested extensive changes to the Microbiology labeling for Bactroban Ointment following the approval of two related NDAs, one for Bactroban Nasal (NDA 50-703) and one for Bactroban Cream (NDA 50-746). *See* Tab 2. The labeling for Bactroban Nasal states that the product has been shown to be active against most strains of MRSA in clinical studies of nasal colonization. The microbiology labeling for Bactroban Ointment is supported by *in vitro* data plus additional *in vitro* and clinical studies submitted to the agency in support of labeling for Bactroban Nasal.

6/ The Clay-Park product is not based on a PEG formulation. It is GSK's understanding that this difference in formulation from Bactroban Ointment, the reference product, necessitated the submission of an application under section 505(b)(2).

approved Microbiology labeling for Bactroban Ointment. Without the "same [Microbiology] labeling," approval under section 505(j) is barred.

b. The Clay-Park Decision Applies to "Q1/Q2" Products

Under 21 CFR 314.94(a)(9)(v), FDA generally requires that topical products submitted under section 505(j) contain the same inactive ingredients as the listed drug. *See also* 21 CFR 314.127(a)(8)(i) and (ii). Often, such products are formulated to contain the same inactive ingredients in essentially the same quantity or ratio as the listed product. Such products are described as being qualitatively (Q1) and quantitatively (Q2) the same as the listed product. A proposed generic mupirocin ointment product that is formulated to be Q1 and Q2 the same as Bactroban Ointment will still be subject to the same limitations discussed in section 3.a., above. That is, an equivalence study in impetigo patients cannot be used to support the full Microbiology labeling, including the MRSA labeling that has been approved for Bactroban Ointment.

A showing of sameness on Q1 and Q2 does not predict sameness with respect to physical properties that are relevant to the clinical equivalence of topical drug products. The structural or physical characteristics of a topical drug product ("Q3") are highly dependent on the precise manufacturing process.7/ According to Dr. Jonathan Wilkin, Director of FDA's Division of Dermatologic and Dental Drug Products, "[e]ven when Q1 and Q2 are identical, the product may have very different physical properties, *e.g.*, viscosity, which may affect product performance."8/ As Dr. Wilkin explained at the March 12, 2003, ACPS meeting:

> Now, traditionally the focus has been limited to what everyone calls Q1 and Q2. Qualitative sameness. It's the list of ingredients. Quantitative sameness, those ingredients are there in the same amounts as found in the innovator. But a noticeable

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7/ *See* J. Wilkin, M.D., *Generic Topical Dermatologic Drug Products: Issues and Opportunities*, www.fda.gov/ohrms/dockets/ac/03/slides/3926S1_17_Wilken.ppt (Mar. 12, 2003) at 4.

8/ *Id.* at 7.

> difference in vehicle properties can also come from Q3, if you will, structural or the phasic differences. *It depends on how one actually manufactures a product that leads to the structural attributes.*

ACPS Transcript at 206-07 (emphasis added).

For example, variability in the manufacturing of topical products, and in the source of bulk ingredients, raises doubts about suppositions of Q3 equivalence for proposed generics. Even if a new mupirocin product is formulated with PEG, the same base used in Bactroban Ointment, significant and clinically meaningful differences in the product can occur. *See id.* And, a sponsor may choose from a number of suppliers of bulk ingredients using a wide range of formulations.9/ Impurities in bulk ingredients may affect product performance; different excipients may contain different impurities, with different clinical impacts. *See* Crowley, PJ, and Martini, LG, *Drug-excipient Interactions*, Pharmaceutical Technology Europe, 13(3), 26-28, 30-32, 34 (2001).

With regard to the manufacturing of mupirocin products, a supplier may use heated tanks to maintain solid polyethylene glycols in a molten state; if so, "[t]he temperature must be kept to the minimum necessary to ensure fluidity." Handbook of Pharmaceutical Excipients, 3rd Ed., 392-398, A.H. Kibbe, ed. (2000). A different temperature specification can yield a different product. Even the mode of mixing the mupirocin ointment could have an impact on efficacy. For example, mixing could result in the active moiety being in a solvated state or in precipitation out as crystals. Clinically, that deviation could result in different rates of absorption in the affected tissues and, hence, different degrees of efficacy. *See* ACPS Transcript at 208 (explaining why, in the manufacture of topical drug products, "[j]ust one simple step in manufacturing can make a substantial difference").

9/ In comparing a product containing PEG to one that does not, it is important to consider that mupirocin is fully dissolved in the Bactroban Ointment formulation. Although typically a drug in solution is most vulnerable to degradation – *e.g.*, hydrolysis and oxidation – PEG serves to stabilize the drug, reducing potential degradation.

In short, such variables in supply and manufacturing may affect product viscosity and other key characteristics of a topical product like mupirocin ointment. It is well known that product viscosity can affect drug release from topical products.10/ Different rates of drug release can, in turn, affect drug availability and efficacy. In all, when determining whether one mupirocin ointment product may receive the same labeling as another, it is not enough to consider Q1 and Q2 "sameness." Rather, as agency officials have recently explained, Q3 sameness is also material to the analysis.

Finally, in a recent response to a citizen petition regarding a topical drug product, the agency indicated that a demonstration of bioequivalence in one indication will confer approval for other related indications, provided the test and reference formulations are Q1 and Q2 the same. 11/ FDA, however, provided no support for the proposition that Q1 and Q2 equivalence for topical drug products allows for extrapolation beyond the specific endpoints in a comparative clinical study. *Compare* ACPS Transcript at 206-08 (explaining that even when Q1 and Q2 are identical, the products can have "incredibly different" properties, depending on the precise way in which they have been manufactured). Very clearly, reliance on Q1 and Q2 to extrapolate beyond the endpoint of an equivalence study in topical products requires further study and analysis before it can be applied beyond the specific situation in that case.

The concerns that led the agency to refuse to approve MRSA and other microbiology labeling for the Clay-Park product apply with equal force to products submitted under section 505(j). The prospect that mupirocin ointment products presented under section 505(j) may be Q1 and Q2 the same as Bactroban Ointment does not support a different result. ACPS Transcript at 208 ("just knowing Q1 and Q2 really does not predict all of those important properties [of topical drug products]").

10/ *See* Jonathan Wilkin, M.D., *Generic Topical Dermatologic Drug Products: Issues and Opportunities, supra*; and Rafiee-Tehrani, M. and Mehramizi, A., *In Vitro Release Studies of Piroxicam from Oil-in-Water Creams and Hydroalcoholic Gel Topical Formulations*, DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 26(4), 409-414 (2000).

11/ *See* Letter from Janet Woodcock, M.D., to John Seager, Westwood Squibb Pharmaceuticals, Inc., Re: Docket No. 95P-0379/CP 1, May 22, 2002.

c. Similar Data Must Undergo the Same Review

Comparative clinical studies with efficacy endpoints will continue to be required to demonstrate the bioequivalence of topical antibiotics like mupirocin ointment, regardless of whether approval is sought under section 505(b)(2) or section 505(j). When reviewing mupirocin products under an ANDA, the agency will confront the same scientific issues it faced in considering the Clay-Park application; the agency must resolve these issues in the same way.12/

This objective can best be accomplished by requiring any subsequent mupirocin applications to be reviewed by the Division of Anti-Infective Drug Products – the review division that was responsible for the review and approval of Clay-Park's product. The Division of Anti-Infective Drug Products is best positioned to evaluate clinical data, develop the agency's policy regarding antibiotic resistance, and formulate appropriate labeling. 13/

Moreover, the general methodological limitations of comparative clinical trials for topical antibiotic products suggest the need for clinical review. The Division of Anti-Infective Drug Products has already developed experience with similar issues in its evaluation of the Clay-Park application. Ultimately, the review division is in the best position in this instance to determine how much can be extrapolated from each sponsor's bioequivalence data to each element of the final labeling.

In short, to ensure consistency of regulatory treatment and outcome, the agency should consolidate the review of comparative clinical studies of mupirocin ointment products before a single group of reviewers in the Division of Anti-Infective Drug Products.

12/ Where similarly situated companies obtain different results based on agency process rather than scientific evidence, the agency's disparate treatment cannot be upheld. *Bracco Diagnostics v. Shalala*, 963 F.Supp. 20 (D.D.C. 1997) (enjoining FDA's disparate treatment of two similar products).

13/ *See, e.g.*, 65 FR 56511 (Sept. 19, 2000); 68 FR 6062 (Feb. 6, 2003).

d. More than One Study is Needed

If FDA concludes that a showing of bioequivalence under section 505(j) could support all elements of the listed product's labeling, FDA must require at least two independent, adequate and well-controlled studies to support the showing of equivalence. As noted above, FDA has not established objective "PK" standards for evaluating the bioequivalence of topical drug products. Rather, sponsors must rely on "appropriately designed comparative *trials*" to show equivalence. 21 CFR 320.24(b)(4) (emphasis added).

The use of the plural "trials" in the regulations plainly requires more than one study. Comparative clinical trials represent the least sensitive and least reliable method of showing equivalence, in part because the endpoints in such studies are more subjective and more susceptible to unanticipated and unsuspected investigational biases.14/ *See generally* Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* at 4-5 (May 14, 1998) (discussing the scientific basis for requiring more than one study to provide "*independent substantiation* of experimental results" (emphasis in original)). This is especially significant for topical anti-infective products, where a significant number of patients enrolled in each study may need to be excluded from the evaluable population because of negative cultures. *See* ACPS Transcript at 192 (noting that "almost half of the study population" may have to be excluded and that "the possibility of false negative cultures has led to some difficulty in interpreting the outcome of these studies . . . .").

For these reasons, the agency drafted the bioequivalence methodology described in 21 CFR 320.24(b)(4) in a markedly different way from the other methodologies described in the same regulation. All of the other specific methodologies in 21 CFR 320.24(b) are drafted in the singular: "An *in vivo* test . . . ." *See* 21 CFR 32024.(b)(1), (b)(2), and (b)(3). The use of the plural "trials" memorializes the requirement that when sponsors use

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14/ In the context of showing bioequivalence oral drug products, FDA has described the comparative clinical trials approach as "insensitive" and urges sponsors to avoid using this method where possible. Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* at 9 (Mar. 2003).

"comparative clinical trials" under section 505(j) to show equivalence, they must be able to reproduce or validate the results of their experiment in at least one additional independent study. 15/

The regulation is binding on both FDA and the public. Moreover, the agency has yet to issue any form of guidance or interpretation on the factors that may allow for a different approach. Thus, while FDA has reserved the discretion to make a finding of bioequivalence based on "[a]ny other approach deemed adequate . . . ." (21 CFR 320.24(b)(4)), the agency has yet to issue guidance on alternative approaches to showing bioequivalence of topical drug products. In short, for mupirocin ointment products under section 505(j), the showing of bioequivalence must be based on at least two adequate and well-controlled clinical studies.

C. ENVIRONMENTAL IMPACT

The actions requested in these comments are not within any of the categories for which an environmental assessment is required pursuant to 21 CFR 25.22.

D. ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted if requested by the Commissioner.

15/ In 1997, Congress amended section 505(d) of the FDCA to allow for the submission of a single study plus "confirmatory evidence" to demonstrate substantial evidence of effectiveness for products submitted under section 505(b). *See* Food and Drug Administration Modernization Act, section 115(a). The agency's Guidance for Industry: *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological* Products (May 1998) outlines the circumstances under which a single clinical study may be sufficient. The Guidance, however, is limited to the "substantial evidence" requirement under section 505(b). *Id.* at 8. The agency has not amended its bioequivalence regulations, nor has it issued guidance, to adopt a "single study" approach to Bioequivalence under 21 CFR 320.24(b)(4).

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

F. CONCLUSION

On behalf of GSK, we request that the Commissioner refrain from approving topical mupirocin products under section 505(j) with Microbiology labeling that differs in material respects from that of the reference product. ANDAs based on data similar to that submitted by Clay-Park must be treated like the Clay-Park product; they must be approved with labeling that differs in critical respects from the labeling that is approved for Bactroban Ointment. As such, these ANDAs must be re-submitted under section 505(b)(2) and, like Clay-Park's product, must be assigned a BX therapeutic equivalence code. Finally, if they are eligible for approval under section 505(j), such products must be supported by two independent clinical trials to establish bioequivalence to Bactroban Ointment.

Respectfully submitted,

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Enclosures